Congenital Chromosomal Syndromes

A Model for Pathogenesis

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■ *The origin of anomalies in the chromosomal syndromes is believed to be both polyetiologic and polypathogenetic. Whereas some malformations quite clearly appear to result from single gene mutations or from genic imbalance due to individual monosomic or trisomic loci, other anomalies (singly or in complex patterns) are better interpreted as originating from disturbances in particular biochemical pathways which affect the development of a variety of traits.*

Additional phenogenetic studies and the use of sophisticated biochemical analysis in persons with complex patterns of anomalies should provide a truer understanding of disease mechanisms and provide guidance for future studies which are aimed at the treatment and prevention of these intriguing misadventures of Nature.

THE G_1 (group 21-22) trisomy syndrome (mongolism) and the D_1-(group 13-15) and E_1-(group 16-18) trisomics exhibit a remarkable variation in the number, pattern and severity of congenital malformations, with very few anomalies being constant. Nonetheless, in the majority of cases it is possible to establish the correct diagnosis clinically.

The malformations are generally believed to originate from the genic imbalance produced by triplicated genes (trisomic loci). Patau and coworkers[13] analyzed the phenotypic characteristics of patients with simple and partial trisomy of chromosomes 18 and D_1 and constructed provisional maps of the trisomic loci.[13] These investigators expressed confidence that "at least some of the main anomalies represent individual trisomy loci and that, by and large, the maps show their true sequence." And in conclusion, they indicated that "the diagnosis of 18 trisomy does not any more require a cytological confirmation."

Phenotypic variability in the chromosomal syndromes, according to Townes and coworkers[21] could be "readily attributed to the innumerable different combination of genes that are possible in a single individual trisomic for a given chromosome."[21] Although others had ascribed this variability to the genetical consequences of "relative homogeneity"[1] and "minimal crossingover,"[6] these conjectures were all based on the assumption that genetic variation of mutation origin was responsible for the many different patterns of anomalies.

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Mutagenesis and Genic Regulation

It is possible to make one clear distinction between the type of mutation that characterizes the chromosomal syndromes and that which typifies the molecular (genic) disorders. In the latter, intragenic aberrations (point mutations) arise from specific *qualitative* changes (base alterations) in desoxyribonucleic acid, while the chromosomal syndromes arise from *quantitative* changes (trisomy or monosomy of genic loci) in otherwise normal desoxyribonucleic acid.[16] Genic mutation in the chromosomal syndromes, while having been proposed by other investigators to account for the phenotypic variableness, probably does not play an essential role, but merely provides variety. Although it is entirely possible that the etiologic disturbances which lead to chromosomal aberrations also act to produce multiple genic mutations, possibly at loci with particular susceptibilities, the usual absence of anomalies in the genetically balanced translocates is evidence that genic mutations are incidental.

Jacob and Monod[5] demonstrated that some structural genes (in certain organisms) appeared to be regulated by *operator* loci. They offered the hypothesis that *operons* (*operator* and structural gene loci) were subject to induction and repression through a composite interaction of *regulator* genes with particular inducer (substrate) and repressor (product) substances. A modification of that hypothesis provides a satisfactory explanation for pathogenesis in certain molecular disorders in man and it has seemed applicable also to the origination of malformations in the chromosomal syndromes.[16,19] Extending their hypothesis to the trisomy syndromes, several investigators have explicated a mechanism to account for the persistence of fetal hemoglobin synthesis in older children with the D_1 trisomy syndrome (see Chart 1).[4,14]

Provocative Observations

Despite any general attractiveness of the foregoing interpretations of pathogenesis in the chromosomal syndromes, certain observations have been made which justify the consideration of alternative or additional mechanisms for the production of congenital malformations. In the case of the chromosomal syndromes, presenting as they do with rather complex patterns of anomalies, it is not surprising that skepticism was expressed when

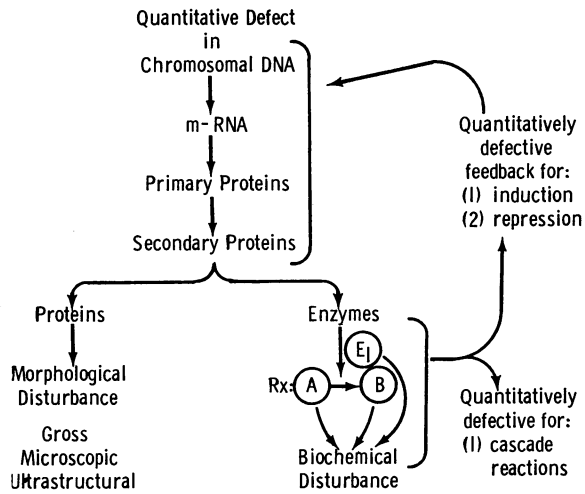

Chart 1.—Proposed model for the origin of malformations in the chromosomal syndromes when trisomic or monosomic loci are responsible. Biochemical disturbances may result from a quantitative change in substrate(A), product(B), or reaction enzyme(E_1). Feedback regulation is deficient because of genic imbalance produced by trisomy or monosomy of loci. Normal cascade regulation of nonallelic genes may also be disrupted.

cytogenetic studies of patients with representative clinical features showed normal chromosomes. Patau and coworkers[13] indicated they had "encountered patients with complex patterns of anomalies that resembled the one or the other of the two new trisomy syndromes so closely that any interpretation not involving a common etiology appeared far fetched." Many of their patients did not have microscopically visible chromosomal abnormalities but the investigators had assumed that undetectable insertions or translocations were present.

Suffice to say, there is not general agreement with Patau and coworkers that their patients possessed undetected mosaicisms, hidden translocations or occult insertions. Representative clinical features which are characteristic of the various chromosomal syndromes have now been found in chromosomally normal persons with clinically apparent Klinefelter's syndrome,[15] Down's disease (mongolism),[2] Turner's syndrome,[3,15] and the E_1[12,15,20] and D_1[9] trisomy syndromes. It is of further interest to note that an infant with a group-A(2/3) translocation exhibited the regular anomalies of the E_1 syndrome,[7] an adolescent with a group-C(6/9) translocation presented with the usual features of mongolism,[18] and two children with proven E_1 trisomy had clinical features that were characteristic of the D_1 syndrome.[17] It goes without saying that one inherent difficulty in genetical studies is that of distinguishing between dis-

orders which are closely alike. These disease mimics exist for both non-hereditary conditions (termed phenocopy) and genic mutants (termed genocopy). Deficiencies in plasma thromboplastin antecedent (PTA) and plasma thromboplastin component (PTC) are well known genocopies of antihemophilic globulin (AHG) deficiency hemophilia. Similarly, differentiation between idiopathic hypoparathyroidism, pseudohypoparathyroidism and Turner's syndrome is often difficult and the diagnosis may remain uncertain. One might appropriately ask whether or not children who are diagnosed clinically as having mongolism but who are chromosomally normal should be designated as mongols or be termed "pseudomongols.[18] Unless chromosomal aberrations are demonstrable, it seems worthwhile to distinguish the "pseudo-trisomy syndromes" from those in which chromosomal mutation can be observed, without de-emphasizing the phenotypic similarities.[19]

Analysis of the Anomaly Patterns

If the anomalies in the E_1 or D_1 trisomy syndromes are graphed according to their order of frequency, a rather continuous curve is obtained, and the various malformations occur with frequency values ranging from 1 to 100 per cent. In rare instances only has it been possible to correlate any of the congenital anomalies with those present in the parents, in siblings or in balanced translocates. There is no sound evidence that ordinary dominant or recessive genic mutations play a significant role in phenotypic development of the chromosomal syndromes. Many of the anomalies (short fingers, syndactyly, polydactyly, simian creases, harelip and ocular defects) do not show bilateral symmetry, an observation which has been generally interpreted as indicative of environmental influences.

Furthermore, when comparative analysis is made of the entire group of defects which have been reported in these autosomal trisomies (see Chart 2), the anomalies can be divided into seven major categories according to their occurrence in one or more of the syndromes. Some anomalies are encountered in all three syndromes, while others are either shared with another disorder or occur separately. The degree of overlap of these complex patterns of anomalies is sufficiently great that it must be seriously questioned whether or not there are individual trisomy loci for each of the anomalies in these three syndromes.

Model of Pathogenicity for Complex Anomaly Patterns

Rather than conclude that separate loci are present for the numerous anomalies in the complex malformation syndromes, it is suggested that certain malformations do not have their origin in mutation of separate genic loci, but instead arise somewhat indirectly because of aberrations in particular metabolic pathways which normally govern the expression of a great number of genes

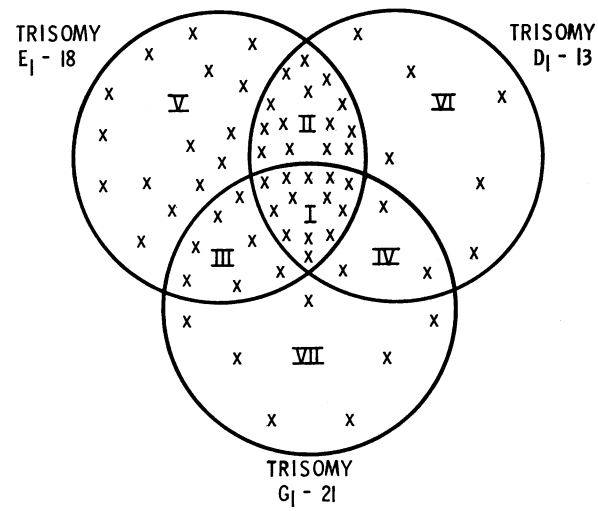

Chart 2.—Schematic representation of anomalies in the D_1-13, E_1-18, and G_1-21 trisomics, showing that some features are unique while others are variously distributed among the three syndromes. Roman numerals refer to anomalies possessing a particular distribution in these syndromes. Each cross(X) represents one of sixty-four different anomalies which have been recorded in these trisomics. Group I anomalies may be present in all three disorders, while those in groups II to IV are shared by two syndromes, and those in groups V to VII are unique to one particular syndrome.

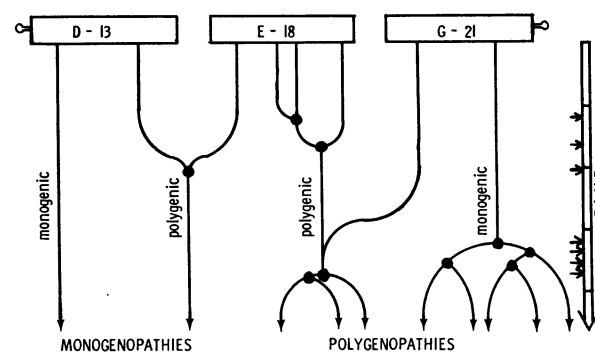

Chart 3.—Possible genic pathways of development for particular traits. Pathways may be controlled by single genes(monogenic) or multiple genes(polygenic). Aberration of a pathway can produce single anomalies(monogenopathy) or multiple anomalies(polygenopathy). Some of the pseudo-chromosomal syndromes may be monogenic polygenopathic conditions. A time scale denotes different times of gene activation and trait development.

which may reside not only on the trisomic or monosomic chromosome but elsewhere in the genome. Depending upon the number of chromosomal or genic loci affected, the pathways can be classified as monogenic (single gene) or polygenic (multiple genes); this is illustrated in Chart 3. The phenotypic expression of a pathway of either type may be monogenopathic (single trait) or polygenopathic (multiple traits). A variable degree of genic activity during different periods of embryogenesis would be possible if the polygenic pathways had several regulatory loci. Aberration of the metabolic pathways could arise from single genic mutations, genic imbalance due to trisomic or monosomic loci, antagonism or synergism of biochemical pathways governed by nonallelic genes or faulty supply and regulation of exogenously governed metabolites. It appears likely that an excess or deficiency of a single component essential to a complex metabolic pathway could invoke multiple malformations. These proposals could satisfactorily account for the sharing of complex patterns of anomalies by the different chromosomal syndromes and also explain their occurrence in cases which are chromosomally normal (pseudochromosomal syndromes).

In favor of the hypothesis are animal studies which have demonstrated the regularity with which certain vitamin deficient diets, vitamin antagonists, and other teratogens may produce more or less characteristic patterns of anomalies.[11] The similarities between these induced patterns of anomalies and those which are found in the chromosomal syndromes have been previously noted.[19] Additionally, discovery of a pathway alteration of the type required for this model of pathogenesis was recently described by McCoy and Chung.[10] They demonstrated a relative pyridoxine deficiency in nonpyridoxine supplemented women in pregnancy and a disposition for pyridoxal depletion in mongols. Their observation of a specific metabolic alteration in pregnancy provides support for the previous suggestion that phenotypic variability in the chromosomal syndromes may be governed by the flux of essential metabolites which control embryonic development.[16,19] The specific requirements for these regulatory metabolites (vitamins, hormones, enzymes and the like) will vary according to the stage of pregnancy, maternal nutritional status and the genetical composition of the mother and fetus. It is believed that the autosomal trisomy states impose particular metabolite deficiencies during the critical periods of embryogenesis.[16] Mongol children have also been shown to have a deficient excretion of 5-hydroxy indoleacetic acid, indol acetic acid and xanthuneric acid, both before and after tryptophane loading.[8]

It is reasonable to believe that additional metabolic disturbances will be found in pregnancy and in the new numerous chromosomal syndromes. It is further suggested that identical or analogous biochemical aberrations will be found to play causative roles in the pathogenesis of malformations in chromosomally normal persons having complex anomaly patterns. In constructing a model of pathogenesis based on the scheme in Chart 3, it is apparent that a minimum of four to seven metabolic "final common pathways" would be required in order to satisfy the hypothesis. However, as additional malformation syndromes are analyzed with respect to the trisomy syndromes, it is likely that upward to 10 or 20 different metabolic pathways could be subject to aberration. For example, the defects which are common to both the Turner XO and the E_1 syndromes might have origin from the same monogenic polygenopathy, and the similarities between the chromatin-negative and chromatin-positive cases of Klinefelter's syndromes could also result from a polygenopathic state.

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